PostScript

LETTERS

Vacuolar leucoencephalopathy and pulvinar sign in association with coeliac disease

Several neurological disorders have been described in association with coeliac disease, including epilepsy, myoclonus, ataxia, myelopathy and peripheral neuropathy. Disorders of white matter have been reported but are rare.[1] We report the clinical, radiological and pathological findings of a man with coeliac disease, progressive neurological decline and spongiform white matter degeneration.

Case

A 55-year-old man presented with anxiety, headache and left upper limb jerking. Coeliac disease had been diagnosed 6 months previously after small bowel biopsy showing positive tissue transglutaminase antibodies. There was no medical history. The patient was not taking any drugs and there was no history of substance misuse. His daughter also has coeliac disease but is neurologically normal. Magnetic resonance imaging (MRI) of the brain and electroencephalogram (EEG) were normal and the patient was started on oral anticonvulsants. He re-presented 2 months later, with increasing anxiety, tremulousness, ataxia, confusion and focal onset seizures becoming secondarily generalised. On examination, he was agitated and was tremulous at rest. He looked about vaguely but was capable of following a 1-step command. Extraocular movements were full, with no nystagmus. Reflexes and plantar responses were normal. He had ataxia and dysmetria on finger-nose-finger testing and a broad-based gait. Sensation was intact. He deteriorated and developed tonic–clonic seizures, requiring intensive care unit admission. Repeat MRI of the brain showed diffuse abnormality of the white matter. Brain biopsy showed mild, non-specific abnormalities. He gradually improved and was discharged seizure free on oral anticonvulsants. One month later, he re-presented with general decline, increasing confusion and agitation. He developed refractory seizures unresponsive to thiopentone and multiple anticonvulsants. An extensive search for an infective, hereditary, paraneoplastic, metabolic or toxic cause was unrewarding. Immunosuppressive treatments, including steroids or immunoglobulin, did not lead to clinical improvement. After a prolonged stay in the intensive care unit, he developed septicaemia and died 6 months after initial presentation.

Results

MRI of the brain was initially normal. Repeat imaging 3 months later showed diffuse, non-enhancing, cerebral white matter changes (fig 1A). Pre-terminally, bilateral posterior thalamic hyperintensities were noted, raising the possibility of variant Creutzfeldt–Jakob disease (vCJD; fig 1B,C). Cerebrospinal fluid (CSF) was acellular with an increased protein concentration of 2437 (200–400) mg/l. Oligoclonal bands were negative. Results of haematological and biochemical tests were normal, as was a full autoantibody screen including thyroid-specific antibodies. Vitamin B_{12}, folate, copper studies, serum ammonia, lactate, pyruvate, serum and urine toxicology, urinary organic acids, very long chain fatty acids, arylsulphatase A, porphyria screen, serum and CSF anti-neuronal and anti-voltage-gated potassium channel antibodies were normal. HIV, herpes simplex virus, JC virus, treponemal and Borrelia serologies were

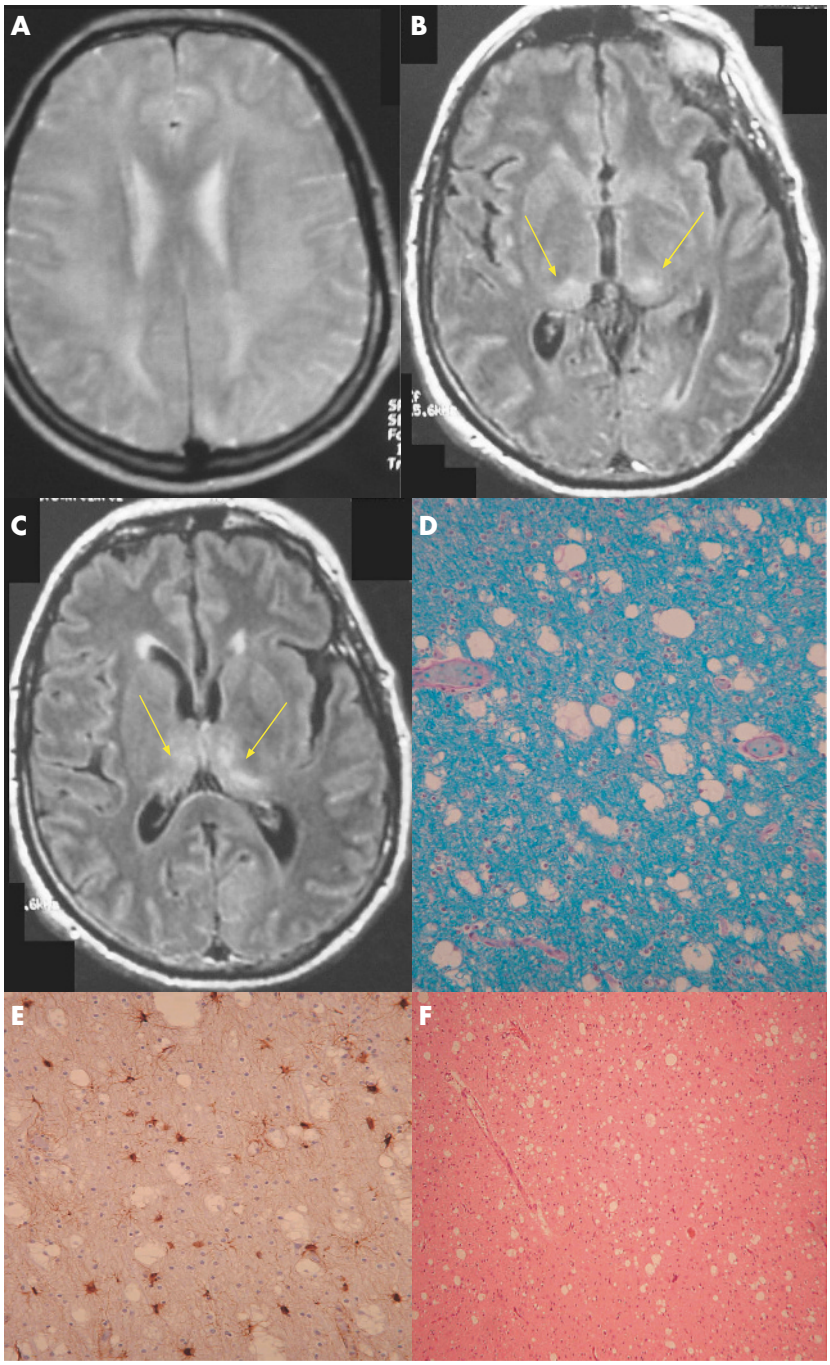

Figure 1 Axial T2-weighted magnetic resonance imaging at 3 months showing diffuse, symmetrical white matter changes in the frontoparietal region. (B, C) Axial FLAIR sequence at 6 months (post right frontal biopsy) showing high signal in the medial and posterior thalami bilaterally (arrows). (D) Vacuolar change in the centrum semi-ovale (Luxol-Fast Blue) with (E) astrocytic hyperplasia (neurofilament). (F) Vacuolar change in the thalamus (haematoxylin and eosin).

negative, as were CSF cultures and 14-3-3 protein. EEG initially recorded a generalised slowing. Subsequently, there were continuous spike and wave discharges consistent with generalised status epilepticus and, later, a burst-suppression pattern.

The cerebral cortex and hippocampus were normal. Profound abnormality of the subcortical white matter was reported, with widespread vacuolar change in the frontal and parietal lobes (fig 1D). Associated astrocytic hyperplasia was observed, but no atypia or inclusions (fig 1E). The thalami showed severe vacuolar change with intense astrocytic hyperplasia (fig 1F). The only other area of grey matter affected was the cerebellar dentate nucleus. The brainstem and cerebellar white matter were normal. No inflammation was seen. vCJD was excluded by negative prion protein immunohistochemistry and western blot. No plaques were seen. Histological examination of the small bowel showed partial villous atrophy consistent with coeliac disease.

Discussion

The question of a putative link between neurological disorders and coeliac disease is the subject of much debate. White matter abnormalities on MRI have been shown in patients with coeliac disease, but the pathology is limited.[1] Postmortem studies have shown several histological abnormalities, including cerebellar Purkinje cell loss and spongiform demyelination in posterior and lateral columns.[2] In our patient, there was extensive vacuolar change in the thalamus and subcortical white matter. One similar report in the literature describes a progressive leucoencephalopathy in association with coeliac disease. Brain biopsy in that case showed myelin pallor, accumulation of CD68-positive macrophages and preservation of axons.[3]

Other causes of vacuolar leucoencephalopathy were considered, including vCJD, HIV infection and glutaric acidaemia, all of which were excluded by appropriate laboratory tests. Toxins and recreational drugs can cause similar changes, but careful inquiry and negative toxicology excluded these causes. The possibility that the changes were seizure related was also considered, but the neuropathology of refractory seizures is well documented and has never shown such spongiform myelinopathy. Furthermore, the hippocampus and cortex showed no evidence of structural injury. We ascribe this patient's leucoencephalopathy to coeliac disease for the following reasons: no other cause for spongiform white matter degeneration could be found; coeliac disease is known to be associated with white matter abnormalities; pathological studies have described spongiform demyelination in patients with coeliac disease; and there is striking resemblance to a previous report.[3]

The radiological findings late in the course of the illness raised the possibility of vCJD. The pulvinar sign, defined as ''hyperintensity of the pulvinar relative to the signal intensity of the anterior putamen'' is a highly accurate diagnostic sign for vCJD in the appropriate clinical setting.[4] Bilateral thalamic hyperintensities have been described in other conditions and may be a source of diagnostic confusion. Our patient had a progressive disorder of >6 months duration, with early psychiatric symptoms (anxiety), ataxia, myoclonus and dementia. EEG did not show typical appearances of sporadic CJD, and MRI showed bilateral pulvinar hyperintensities. Although his clinical presentation was atypical, we could not exclude the possibility of vCJD until after a neuropathological examination.

The pathogenesis of neurological complications in coeliac disease remains unknown. Dietary and immune-mediated mechanisms have been suggested, but conclusive evidence is lacking. Interestingly, raised CSF glycine may be associated with similar white matter disease.[5] A relationship between intestinal malabsorption and disturbed amino acid metabolism could, in theory, result in the exposure of white matter to altered levels of amino acids, which may have been toxic. Further CSF was unfortunately not available to measure glycine levels in this patient.

The spectrum of neurological complications associated with coeliac disease continues to expand. We suggest that coeliac disease be considered in the differential diagnosis of leucoencephalopathy of unknown origin and that it may be a cause of a false positive pulvinar sign.

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Informed consent was obtained for publication of the patient's details described in this report.

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Mitochondrial disease mimicking Charcot–Marie Tooth disease

Patient 1 was a 24-year-old woman with a 12-year history of a progressive sensorimotor peripheral neuropathy associated with pes cavus and bilateral foot drop. She had no family history of neuromuscular disease. At the age of 20 years she underwent nerve conduction studies (NCS), which showed absent motor and sensory responses in the lower limbs, with reduced upper limb motor conduction velocities (table). Upper limb sensory nerve action potentials (SNAP) were also absent. Interestingly, she had a lumbar puncture that showed no cells but a raised protein concentration of 1.56 mmol/l. A sural nerve biopsy showed active chronic axonal neuropathy with some segmental demyelination, not consistent with chronic inflammatory demyelinating polyneuroapthy (CIDP). Her muscle biopsy showed neuropathic changes with a mild inflammatory infiltrate. Genetic testing for X-linked Charcot–Marie Tooth disease (CMT) 1A, 1B and X-linked was negative. Four years later, she developed an external ophthalmoplegia, increasing abdominal borborygmi, pain, nausea, vomiting and diarrhoea, associated with considerable weight loss. Urinary thymidine levels (92 μmol/mmol creatinine) and deoxyuridine (168 μmol/mmol creatinine) were markedly raised. DNA sequencing showed compound heterozygotic mutations (G106T and del-G at nucleotide 1444) in the thymidine phosphorylase gene, confirming the diagnosis of mitochondrial myopathy, neuropathy and gastrointestinal encephalopathy (MNGIE) syndrome.

Patient 2 is a 38-year-old man who first noticed weakness and cramping of his legs at the age of 27 years. NCS carried out at the time of presentation showed mildly reduced motor amplitudes and slowed motor conduction velocities (table), worse in the lower limbs than in the upper limbs, suggestive of a demyelinating rather than axonal peripheral neuropathy. SNAPs were absent in the lower limbs, but were normal in the upper limbs. The diagnosis of CMT was made on the basis of the clinical and neurophysiological findings, but genetic testing did not confirm this diagnosis. At the age of 35 years, the patient began to develop cramping abdominal pains associated with a decrease in appetite, early satiety and marked weight loss. He recalled having prominent borborygmi throughout childhood. He is the third of four boys, whose parents are first cousins. His second eldest brother had diabetes and died at the age of 27 years from a ''ruptured diverticulum''. On examination, he was markedly cachectic, with bilateral pes cavus and clawed toes. He had an external ophthalmoplegia with bilateral ptosis, and facial, proximal and distal limb muscle weakness. He had low thymidine phosphorylase activity in the buffy coat, associated with an increased concentration of plasma thymidine (11.9 μmol/l) and deoxyuridine (6.7 μmol/l). DNA sequencing showed a homozygotic 20 base-pair deletion in exon 10 of the thymidine phosphorylase gene, thus confirming the diagnosis of MNGIE syndrome.

Patient 3 is a 30-year-old man, with no family history of neuromuscular disease. At age 25 years, he presented with walking difficulties, muscle weakness and exercise intolerance. On examination, he had evidence of peripheral wasting, clawed toes and bilateral pes cavus. His upper and lower limb motor